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Letters to the Editor

Calcium channel blocker use and gastrointestinal tract bleeding among older adults

SIR—Several studies have reported that the incidence of gastrointestinal (GI) tract bleeding is increased about two-fold in people using calcium channel blockers (CCBs) [1–3] CCBs have powerful vasodilatory effects They may also affect platelet function [4] and red blood cell deformability [5] when taken orally at standard doses Therefore, the hypothesis that these agents may increase the risk of bleeding is biologically plausible We conducted an ancillary study in the Cardiovascular Health Study (CHS) cohort of older adults to examine the association between the use of CCBs and GI bleeding

The CHS is a prospective cohort study established in 1989/90 of 5,888 people aged 65 years and older in four communities in the United States of America, selected from Medicare eligibility lists [6] At study baseline and annually during follow-up, participants completed questionnaires that included information about their medical history and were examined at a study clinic Medication use was collected by an inventory method at baseline and at annual intervals Hospital admissions were identified from several sources, including Medicare billing records and semi-annual subject contacts We identified and validated via chart review all hospitalizations from study baseline during March 1998 containing discharge diagnoses for gastric, duodenal, peptic, or gastrojejunal ulcer with bleeding, rectal bleeding, haematemesis, melaena, or GI bleeding not otherwise specified We excluded bleeding events that occurred after the third day of hospitalization, or that were due to a procedure or surgery We were not able to capture non-hospitalized GI bleeding in this study

During an average follow-up of 5 1 years, we identified 121 validated hospitalized GI bleeding events in treated hypertensive subjects that were confirmed upon review (32% of potential events were not confirmed) Hypertensive subjects who used CCBs had an incidence of GI bleeding of 9 9/1,000 person-years, compared with a rate of 6 1/1,000 person-years in those who used other antihypertensive agents [age-adjusted Cox hazard ratio=1 62, 95% confidence interval (CI)=1 13–2 32] After also adjusting for cardiovascular disease history, the hazard ratio associated with CCB use was 1 37 (95% CI=0 95–1 98) Further adjustment for GI bleeding risk factors such as sex, aspirin use, and oral anticoagulation had little effect Analyses limited to subjects who received monotherapy for hypertension found that CCB users tended to have a higher incidence of bleeding than subjects using other types of antihypertensive medications, though results were not statistically significant Higher CCB doses were not associated with higher bleeding risk, on the contrary, those using lower doses had higher risk Each of the three major CCB types (dihydropyridines, phenylalkylamines, and benzothiazepines) was associated with a slight but non-significant elevation in risk, and the hazard ratio was 1 85 for immediate-release CCB formulations and 1 17 for sustained-release CCB formulations When we limited the analysis to events that met pre-specified criteria for 'life-threatening' bleeding (n=45 events), the hazard ratio associated with CCB use was 1 98 (95% CI=1 08–3 63) The hazard ratio associated with CCB use was not significantly different across strata defined by use of other medications, suggesting an absence of synergism

In summary, among hypertensive subjects 65 years and older in an epidemiological cohort study, there was a 62% increase in risk of GI tract bleeding among users of CCBs, but after adjusting for pre-existing cardiovascular disease, the increase in risk was 37% and was of borderline statistical significance An important limitation of this observational study is the lack of random assignment of CCBs and other antihypertensive medications Some randomized placebo-controlled controlled trials have suggested an increased occurrence of bleeding events with CCBs [7, 8], while others have not [9] We note that incomplete ascertainment of bleeding events may have limited the ability of previous clinical trials to assess adequately whether CCBs cause bleeding complications For example, the overall incidence of all types of bleeding (excluding cerebral or retinal haemorrhage) reported among the hypertensive patients 60 years or older in the Syst-Eur nitrendipine trial was 3 3/1,000 person years [9] By contrast, in the present cohort of older adults with hypertension, we found an incidence of 7 5/1,000 person-years for hospitalized gastrointestinal bleeding alone Even a relatively low rate of bleeding complications might affect the overall balance of risks and benefits of CCB therapy in older patients with hypertension For this reason, it would be prudent to include bleeding as a pre-specified, prospectively collected endpoint in ongoing and future randomized controlled trials of calcium channel blocking-agents

ROBERT C KAPLAN, SUSAN R. HECKBERT[1], THOMAS D. KOEPSELL[1], FRITS R. ROSENDAAL[2], CURT D FURBERG[3], LAWTON S. COOPER[4], BRUCE M. PSATY[1], FOR THE CARDIOVASCULAR HEALTH STUDY INVESTIGATORS

Department of Epidemiology and Social Medicine,
Albert Einstein College of Medicine,
Belfer Building Room 1308C,
Bronx NY 10461, USA
Fax (+1) 718 430 8780
Email. rkaplan@aecom yu edu
[1]*Cardiovascular Health Research Unit,*
Seattle WA 98101–1448, USA
[2]*Department of Clinical Epidemiology,*
Leiden University Medical Center,
Leiden, The Netherlands
[3]*Department of Public Health Sciences,*
Wake Forest University School of Medicine,
Winton-Salem NC 27157–1063, USA
[4]*NHLBI Division of Epidemiology & Clinical Application,*
Prevention Studies Research Group,
Bethesda MD 20892–7936, USA

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